alkoxycarbonylalkylaminoalkyl, alkoxycarbonylaminoalkyl, optionally substituted phenyl, optionally substituted pyridin-2-yl or optionally substituted 5-or 6-membered cycloalkyl, acylaminoalkyl, alkylaminoalkylacyloxyalkyl or

the group (R^2, R^3)N- may form an optionally substituted pyrrolidine, pyrrolidone or piperidine; and

X^- is a pharmaceutically acceptable anion,

or a pharmaceutically acceptable salt thereof.

2. (amended) Compounds of claim 1 wherein R^3 is alkylaminoalkyl, alkylcarbonyl, alkylcarbonyloxyalkyl, alkylaminoalkylcarbonyloxyalkyl, substituted phenyl, substituted pyridin-2-yl or substituted 5-or 6-membered cycloalkyl.

30. (amended) A pharmaceutical composition for use as an antifungal, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

REMARKS

Claims 1-31 are pending, claims 12, 19-21, 25, and 28-29 were withdrawn subject to a restriction requirement, and claims 1-11, 13-18, 22-24, 26-27 and 30-31 were rejected in the above-identified patent application. Applicants have amended claims 1, 2, and 30 and have not deleted or added any new claims. Accordingly, claims 1-11, 13-18, 22-24, 26-27 and 30-31 are presently being examined.

Support for the Amendments0

Applicants have amended claims 1, 2, and 30 in order to more clearly describe and distinctly claim the subject matter of applicants' novel water-soluble azole compounds of formula (I). Specifically, applicants have amended claims 1, 2, and 30 in order to

overcome the Examiner's rejections under 35 U.S.C. §112, first and second paragraphs. These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accord with 35 U.S.C. §132. Accordingly, applicants request entry of these amendments.

Election/Restriction

The Examiner has made final the restriction requirement. The Examiner states that applicants' election of Group I and the species of example 7 is acknowledged but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. The Examiner has examined this application with regard to the elected compound, wherein Q represents (2R, 3R)-3 -[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1, 2, 4-triazol-1-yl)-butan-2-ol, R3 is (optionally substituted) pyridin-2-yl and R1, R2 and X as set forth in claim 1, exclusively.

Rejection of Claims 1 and 2 under 35 U.S.C. §112, first paragraph.

The Examiner has rejected claims 1 and 2 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner states that the expressions "optionally substituted, "solvates" and "derivative with antifungal ...azole" in claims 1 and 2 are employed throughout the claims with no indication given as to what the substituents, solvates and derivatives really are. Applicants' claims as amended obviate the Examiner's rejections.

As set out above, applicants have amended claims 1 to delete reference to "hydrates or solvates" and have amended claim 2 to delete reference to "optionally". Accordingly, the Examiner's rejection of claims 1 and 2 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Rejection of Claims 1-11, 13-18, 22-24, 26 and 30 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claims 1-11, 13-18, 22-24, 26 and 30 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the use of plurals on "salts, hydrates, solvates and compounds makes claims 1-11, 13-18, 22-24, and 26 read on mixtures rather than specific compounds. The Examiner further states that the phrase "as well as... formula (I)" is not written in alternative language and suggests instead the phrase "or a pharmaceutically acceptable salt.... formula(I)". Regarding claim 30, the Examiner states that the phrase "in particular" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. Applicants' claims as amended obviate the Examiner's rejections.

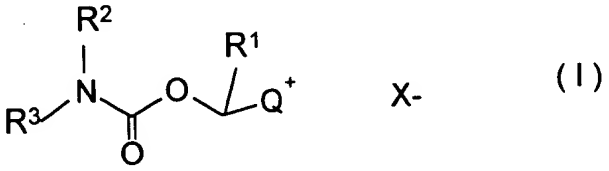
As set out above, applicants have amended claims 1 to delete reference to "hydrates or solvates" and have amended claim 2 to delete reference to "optionally". Applicants have further amended claim 1 to recite the phrase "or a pharmaceutically acceptable salt thereof". Applicants have also amended claim 30 to delete reference to "in particular". Accordingly, the Examiner's rejection of claims 1-11, 13-18, 22-24, 26 and 30 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Rejection of Claims 1-11, 13-18, 22-24, 26, 27, 30, and 31 under 35 U.S.C. §102(a), (e) and/or (f) as being anticipated by *Hayase et al.*

The Examiner has rejected claims 1-11, 13-18, 22-24, 26, 27, 30, and 31 under 35 U.S.C. §102(a), (e) and/or (f) as being anticipated by United States patent no. 6,300,353 (*Hayase et al.*). The Examiner states that *Hayase et al.* specifically recites the compound (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)-2-2,5-difluorophenyl)-1-(lH-1,2,4-triazol-1-yl)-

butan-2-ol (column 5, lines 5-6). The Examiner contends that the precursor and final product are not different products, regardless of differences in their activity and efficacy and hence, the instant compound is deemed to be anticipated therefrom. Applicants traverse the Examiner's rejection.

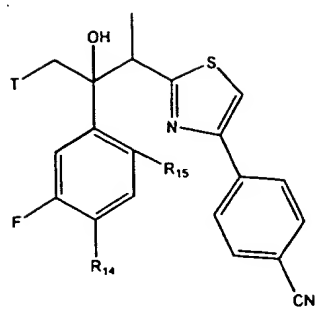
The present invention relates to novel water-soluble azole compounds useful for the treatment of systemic mycoses and suitable for both oral and particularly parenteral administration, a process for their manufacture, antifungal compositions containing them and a method for treating mycoses. More particularly, the present invention refers to compounds of formula (I),



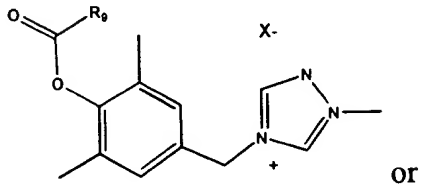
(I)

wherein Q is a 3H-imidazole or 1, 2, 4-triazole derivative with antifungal activity which is linked to the remainder of the compound of formula (I) by a nitrogen in the azole; R^1 is hydrogen or alkyl; R^2 is hydrogen, alkyl, alkylcarbonyloxyalkyl, alkoxycarbonyl, alkylcarbonyl, mono- or dialkylaminoalkylcarbonyloxyalkyl; R^3 is alkylaminoalkyl, alkylcarbonyl, alkylcarbonyloxyalkyl, alkylaminoalkylcarbonyloxyalkyl, hydrogen, acylalkylaminoalkyl, alkyl, hydroxyalkyl, aminoalkyl, alkylcarbonylaminoalkyl, alkylcarbonylalkylaminoalkyl, alkoxycarbonylalkylaminoalkyl, alkoxycarbonylaminoalkyl, optionally substituted phenyl, optionally substituted pyridin-2-yl or optionally substituted 5-or 6-membered cycloalkyl, acylaminoalkyl, alkylaminoalkylacyloxyalkyl or the group (R^2, R^3)N- may form an optionally substituted pyrrolidine, pyrrolidone or piperidine; and X^- is a pharmaceutically acceptable anion, or a pharmaceutically acceptable salt thereof..

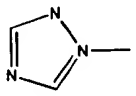
The *Hayase et al.* reference discloses compounds of the formula:



wherein R^{14} and R^{15} are each independently hydrogen or fluorine and T is a group of the formula:



or



wherein R^9 is pyrrolidinyl or a group A-NH-B, wherein A is hydrogen or straight chain or branched -C_1-C_5 alkyl; and B is straight chain or branched -C_1-C_4 alkylene, -CH_2CONHCH$_2$ or -$CH_2CH_2CH_2$-CH(NH_2).

Contrary to the Examiner's position, applicants submit that the compounds of the present invention are not anticipated by *Hayase et al.* *Hayase et al.* discloses compounds such as (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)-2-2,5-difluorophenyl)-l(lH-1,2,4-triazol-1-yl)-butan-2-ol, which compound is not claimed within the present invention. The compounds of the present invention are carbamate derivatives, (R^2R^3N(C=O)OCH(R^1)-), of the above-mentioned compound. There is no teaching in *Hayase et al.* to make the carbamate derivatives of the present invention.

Accordingly, the Examiner's rejection of claims 1-11, 13-18, 22-24, 26, 27, 30, and 31 under 35 U.S.C. §102(a), (e) and/or (f) as being anticipated by *Hayase et al.* should be withdrawn.

Rejection of Claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 under 35 U.S.C. §103(a) as being unpatentable over *Hayase et al.* in view of *Hudyma et al.*

The Examiner has rejected claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 under 35 U.S.C. §103(a) as being unpatentable over *Hayase et al.* in view of United States patent no. 6,265,584 (*Hudyma et al.*) and J. Med. Chem., 37 (26) 1994 pgs.4423-4429 (*Davidsen et al.*). The Examiner states that *Hayase et al.* discloses the final product having the same use, *Hudyama et al.* teaches that analogous amine salts of triazoles similar to those of the claimed invention retain the activity associated with the final products, and *Davidsen et al.* teaches that pyridine salts are extremely soluble. The Examiner argues that in view of the structural similarity between the compounds of the instant claims and those of *Hayase et al.* and that the substituent connected with the differentiating feature is lost *in vivo*, one of ordinary skill would expect that the claimed compounds would have antifungal activity. Applicants traverse the Examiner's rejections.

As set above, the difference between the present invention and the *Hayase et al.* reference is that a carbamate moiety, $(R^2R^3N(C=O)OCH(R^1)$-), is connected to the compounds of *Hayase et al.* *Hudyma et al.* discloses an amino-phenyl-oxo-oxy-methyl-(oxy-oxo)n-moiety, wherein n is 0 or 1, which is linked via an oxygen atom to the substituted triazole (A). In the present invention, a carbamate moiety with a $-CH(R^1)$-group is attached to the triazole. *Davidsen et al.* discloses $R_2N(C=O)OCH_2$- groups attached to a pyridinium prodrug as being useful for the treatment of inflammation, septic shock, and asthma. *Davidsen et al.* does not claim that the pyridinium prodrugs have antifungal activity. Besides having a new utility, the compounds of the present invention have a carbamate moiety attached to a substituted triazole moiety. There is no teaching within *Davidsen et al.* that such carbamate derivatives would also work with triazole compounds

with antifungal properties. There is no teaching in either *Hayase et al., Hudyma et al.,* or *Davidsen et al.* which would motivate a person stilled in the art to combine the technical features of the mentioned prior art and finally to come to the present invention.

To further support the presence of an inventive step, applicants have filed concurrently herewith a Declaration pursuant to 37 C.F.R. §1.132. In summary, applicants have unexpectedly discovered that the antigenicity of the N-substituted carbamoyloxyalkyl-azolium derivatives of the present invention are negative while the antigenicity of the corresponding underivatized prior art compounds, such as those of *Hayase et al.,* are positive. In the antigenicity study, a series of tests was conducted in guinea pigs, in particular, active systemic anaphylaxis (ASA) tests and passive cutaneous anaphylaxis (PCA) tests were performed. Specifically, the antigenicity studies were performed on the closest prior art compound (pursuant to MPEP §716.02e) of *Hayase et al.* (compound 1, from example 1 on page 16 of *Hayase et al.*) and applicants' compound (compound 2, example c on page 66 of applicants' specification). No positive ASA reaction or PCA reaction was observed in animals immunized with 30 mg/animal of compound 2 plus Freund' s adjuvant (FA) and challenged with 1 mg/animal of compound 2 alone or with 1 mg/animal of compound 2-ovalbumin (OVA) mixture. No positive ASA reaction or PCA reaction was observed in animals immunized with 3mg/animal of compound 2 guinea pig serum albumin (GPSA) mixture plus FA and challenged with 1mg/animal of compound 2 alone or 1 mg/animal of compound 2-OVA mixture. The results from this study show that the antigenicity of applicants' compound 2 was negative. Active systemic anaphylaxis (ASA) tests on the prior art compound of *Hayase et al.,* compound 1, on the other hand, demonstrated that the antigenicity of compound 1 was positive. Accordingly, the studies set out in applicants' Declaration show unexpected results in accord with MPEP §716.02(a).

Hence, the Examiner's rejection of claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 under 35 U.S.C. §103(a) as being unpatentable over *Hayase et al.* in view of *Hudyma et al.* and *Davidsen et al.* should be withdrawn.

Obviousness of a composition or process must be predicated on something more than it would be obvious "to try" the particular component recited in the claims or the possibility

it will be considered in the future, having been neglected in the past. *Ex parte Argabright et al.* (POBA 1967) 161 U.S.P.Q. 703. There is usually an element of "obvious to try" in any research endeavor, since such research is not undertaken with complete blindness but with some semblance of a chance of success. "Obvious to try" is not a valid test of patentability. *In re Mercier* (CCPA 1975) 515 F2d 1161, 185 U.S.P.Q. 774; *Hybritech Inc. v. Monoclonal Antibodies. Inc.* (CAFC 1986) 802 F2d 1367, 231 U.S.P.Q. 81; *Ex parte Old* (BPAI 1985) 229 U.S.P.Q. 196; *In re Geiger* (CAFC 1987) 815 F2d 686, 2 U.S.P.Q.2d 1276. *In re Dow Chemical Co.* (CAFC 1988) F2d, 5 U.S.P.Q.2d 1529. Patentability determinations based on that as a test are contrary to statute. *In re Antonie* (CCPA 1977) 559 F2d 618, 195 U.S.P.Q. 6; *In re Goodwin et al.* (CCPA 1978) 576 F2d 375, 198 U.S.P.Q. 1; *In re Tomlinson et al.* (CCPA 1966) 363 F2d 928, 150 U.S.P.Q. 623. A rejection based on the opinion of the Examiner that it would be "obvious to try the chemical used in the claimed process which imparted novelty to the process does not meet the requirement of the statute (35 U.S.C. 103) that the issue of obviousness be based on the subject matter as a whole. *In re Dien* (CCPA 1967) 371 F2d 886, 152 U.S.P.Q. 550; *In re Wiaains* (CCPA 1968) 397 F2d 356, 158 U.S.P.Q. 199; *In re Yates* (CCPA 1981) 663 F2d 1054, 211 U.S.P.Q. 1149. Arguing that mere routine experimentation was involved overlooks the second sentence of 35 USC 103. *In re Saether* (CCPA 1974) 492 F2d 849,181 U.S.P.Q. 36. The issue is whether the experimentation is within the teachings of the prior art. *In re Waymouth et al.* (CCPA 1974) 499 F2d 1273, 182 U.S.P.Q. 290. The fact that the prior art does not lead one skilled in the art to expect the process used to produce the claimed product would fail does not establish obviousness. *In re Dow Chem. Co.* (CAFC 1988) 5 U.S.P.Q.2d 1529.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. It is not proper within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggest to one of ordinary skill in the art. The references of record fail to teach or suggest applicant's invention as a whole.

In view of the foregoing Amendment and Response, applicants request reconsideration pursuant to 37 C.F.R. §112 and allowance of the claims pending in this application. Applicant requests the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference. No fee is deemed necessary in connection with the filing of this Amendment and Response. If any fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 12-2525.

Respectfully submitted,
Fukuda et al.

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